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Improving Maternal Health and Obstetric Safety in the U.S.

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Janine Austin Clayton, M.D., FARVO
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This issue of Women's Health in Focus at NIH *concentrates on the continuing problem of maternal morbidity and mortality in our country and follows up on topics discussed in issue 2.1 of this publication. In the articles that follow, we describe how the United States has the highest rates of pregnancy-related deaths and severe maternal health complications of any high-income nation. Studies show that at least half of these deaths are preventable. Improving obstetric safety protocols and addressing health disparities, particularly those that disadvantage underrepresented racial and ethnic groups and residents in rural areas, could save women's lives.*

A recent special issue of the Journal of Women's Health*, edited by ORWH Associate Director for Science Policy, Planning, and Analysis Samia Noursi, Ph.D., explores the problem of U.S. maternal morbidity and mortality. ORWH experts, NIH-supported investigators, and others contributed articles and commentaries characterizing factors influencing the problem, suggesting evidence-based solutions, and posing research questions for new avenues of investigation. (See page 10 for more information.)*

Other articles discuss ongoing efforts to combat the coronavirus pandemic, issues facing women in biomedical careers, and other topics. I hope you find this issue informative. Please share it with your colleagues and encourage them to subscribe. Stay safe!

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Federal Health Services Address Maternal Health, Obstetric Safety, and Associated Disparities

In late 2020, the U.S. Department of Health and Human Services (HHS) declared improving maternal health a national priority and released Healthy Women, Healthy Pregnancies, Healthy Futures: Action Plan to Improve Maternal Health in America. The action plan aims to "make the United States one of the safest countries in the world for women to give birth." The HHS plan articulates a life-course approach for improving health outcomes for women of reproductive age, ensuring healthy pregnancies and births, increasing the quality of postpartum care, and strengthening data collection on pregnancy outcomes to bolster research and policy decisions.[1]

The HHS plan also characterizes troubling trends related to maternal health in the United States, where women experience the highest rates of pregnancy- and delivery-related health problems and fatalities among high-income nations. This problem—often called maternal morbidity and mortality (MMM)—has worsened over the past few decades. Between 1987 and 2017, the proportion of reported cases of maternal mortality more than doubled—from 7.2 to 17.3 deaths per 100,000 live births.[2] Some underrepresented racial and ethnic groups experience even higher rates of maternal mortality. Data from 2014 to 2017 show 41.7 deaths per 100,000 live births among Black women and 28.3 deaths per 100,000 live births for American Indian/Alaska Native women.[2] (For more information on these disparities, see "Research Demonstrates Disparities in Maternal Health Outcomes, Suggests Actionable Solutions," page 8.) Causes of death include severe bleeding, infection, blood pressure disorders, and labor and delivery complications.[3] Importantly, research findings reveal that between half and two-thirds of these deaths are preventable.[1,4,5] Further, for every pregnancy-related death in the United States, 70 women experience a "near miss" from severe pregnancy-, delivery-, or postpartum-related complications.[6] U.S. women also experience high rates of short- and long-term health problems resulting from—or coincident with—pregnancy or delivery, such as diabetes, cardiovascular disease, high blood pressure, blood clots, infection, anemia, depression, and anxiety.[3,7] Implementation of clinical checklists prompting providers to act and safety bundles from the Alliance for Innovation on Maternal Health could improve maternal health and save lives.

In response to these troubling health trends, the HHS action plan sets three ambitious targets for the next 5 years: (1) to reduce the maternal mortality rate by 50%, (2) to reduce the low-risk cesarean delivery rate by 25%, and (3) to achieve blood pressure control in 80% of women of reproductive age with hypertension. As part of HHS, NIH contributes to these efforts with new and ongoing initiatives and research support. In issue 2.1 of *Women's Health in Focus at NIH*, we discussed investigations into MMM and some of the programs and practices then in place to mitigate the crisis. Here, we describe recent efforts to improve maternal health and obstetric safety, to address health disparities, and to understand and mitigate the medical, structural, and socioeconomic causes of MMM.

The NIH IMPROVE Initiative Supports Research on MMM

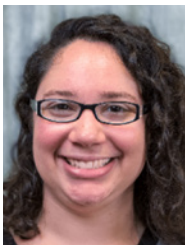
The NIH Office of the Director (OD), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), ORWH, and other NIH Institutes, Centers, and Offices (ICOs) have developed the NIH-wide IMPROVE initiative

(**I**mplementing a **M**aternal health and **PR**egnancy **O**utcomes **V**ision for **E**veryone) to support research on how to reduce preventable MMM; improve health for women throughout pregnancy, delivery, and the postpartum period; and promote health equity in the United States. Plans for the IMPROVE initiative include a multipronged, innovative research program designed to target health disparities and populations disproportionately affected by MMM. This initiative will study geographical disparities and social determinants of health, including level of educational attainment, race, and socioeconomic standing. IMPROVE awarded approximately $7.2 million in research grants in fiscal year 2020 (through NOT-OD-20-104). The initiative uses an integrated approach to understand the biological, behavioral, sociocultural, and structural factors contributing to MMM. This understanding will contribute to an evidence base to inform changes to care and to improve outcomes in specific populations and regions of the country.

NIH Addresses Racial Disparities in MMM

The HHS action plan identifies racial health disparities as key challenges in improving maternal outcomes. ICOs, including the National Institute on Minority Health and Health Disparities (NIMHD), have been addressing these challenges. "A priority of NIMHD is to support original, innovative, multidisciplinary research to advance the understanding, prevention, and reduction of pregnancy-related complications and deaths among disproportionately affected women," wrote Beda Jean-François, Ph.D., and Gina Roussos, Ph.D., of NIMHD.[8] "This includes women from underrepresented racial and ethnic groups, women with underprivileged socioeconomic status, and those living in underserved rural settings."[8]

Beda Jean-François, Ph.D., NIMHD



Gina Roussos, Ph.D., NIMHD

In fiscal year 2020, NIMHD—in collaboration with OD, the National Heart, Lung, and Blood Institute (NHLBI), and ORWH—awarded research grants to six institutions through an R01 funding mechanism (RFA-MD-20-008). These investigations explore the factors underlying MMM that go beyond the level of the individual, such as health care access, health care settings, community resources, and discriminatory practices affecting underrepresented groups. Research funded through this R01 will propose and evaluate the effectiveness of multilevel interventions—at the individual, health care setting, community, and societal levels—to reduce MMM. Studies will analyze how policies and site-of-delivery factors contribute to disparities in MMM and examine peripartum phenotypes of cardiovascular disease risk among Black women. In addition, four research teams funded through this R01 will assess different interventions implementing evidence-based clinical best practices and addressing health care system factors.

NIMHD also supports 22 other innovative projects that align with multiple goals of the HHS plan. These projects include research on how exposure to chemical pollutants and place-based stressors influence health disparities in maternal health (P50-MD-015496), on an intervention to promote healthy lifestyle behaviors among Latina women who develop gestational diabetes (R44-MD-009454), and on the Optimize intervention, which includes an integrated and comprehensive perinatal care checklist for Black women along with patient navigation support (R01-MD-014068). These and other NIMHD initiatives address the multiple research goals outlined by the HHS action plan to improve maternal health outcomes and to reduce MMM disparities.

NIH Supports MMM Research in States with Low NIH Funding

The HHS plan highlights the health disparities that disadvantage pregnant women residing in lower-resourced areas of the United States.[1] Residents in these regions, particularly those from rural areas, have less access to health care, and many suffer from poorer health outcomes than the average American.[9] The medical outcomes of mothers and infants contribute to this trend, and the loss of obstetrics services constitutes a likely causal factor. Only 55% of rural U.S. counties had obstetric units in 2004, and this percentage had decreased to 46% by 2014.[9] Women in rural areas also have higher rates of delaying prenatal care initiation than urban residents.[1] These trends may exacerbate existing neonatal and maternal health problems common in rural areas, such as premature birth, low birth weight, maternal and infant mortality, severe maternal morbidity, and increased risk of peripartum and postpartum depression.

The congressionally mandated Institutional Development Award (IDeA) program builds research capacity in States where NIH funding has been low. ORWH partnered with the National Institute of General Medical Sciences (NIGMS) and other ICOs to expand this program to address women's health and prioritize MMM. Since mid-2020, NIH has awarded $4.8 million to 19 applicants through this program to support research to reduce preventable

maternal mortality; improve health for women before, during, and after delivery; and promote health equity. Research projects funded through this program address a wide range of topics related to women's health as well as maternal and infant morbidity and mortality, such as cardiovascular diseases, alcohol-exposed pregnancies, mobile health interventions to improve maternal morbidity, infectious diseases in pregnant and nonpregnant women, pediatric diseases, and fetal growth abnormalities. More information on the IDeA administrative supplements and a complete list of awardees are available here.

NIH Supports the Study of MMM in Understudied, Underrepresented, and Underreported (U3) Populations of Women

NIH, through ORWH's U3 Administrative Supplement Program, supports research on social determinants of health—such as gender, race, ethnicity, socioeconomic status, and rural/urban residence. The HHS action plan identifies many of these factors as relevant to MMM. Since its inception in 2017, the U3 program has awarded 59 supplemental grants. Twelve MMM-relevant projects have been funded in fiscal years 2017–2020, including projects on insulin resistance; neonatal adiposity and race/ethnicity; sickle cell disease and maternal morbidity; associations among socioeconomic condition, placental modifications, and preterm birth; and biological and social determinants of severe maternal morbidity.

"Often, discussions of MMM disparities emphasize chronic disease vulnerability but neglect relevant effects of the social determinants of health, like poverty, food and housing security, educational attainment, access to health care, and structural racism," said ORWH Health Scientist Administrator and Program Officer Miya Whitaker, Psy.D., M.A. "Unfortunately, inequality is common across our State and national systems, shaping maternal health disparities as well as other public health concerns." Dr. Whitaker adds that ORWH's, NICHD's, NIMHD's, and NHLBI's funding opportunities—as well as the support provided for multilevel and multidisciplinary research targeting MMM reduction—are critical to eliminating the barriers underrepresented and underresourced women face that prevent them from experiencing healthy pregnancies and positive birth outcomes.

The Surgeon General Issues a Call to Action

The Office of the Surgeon General issued a call to action to coincide with the release of the HHS maternal health action plan. Whereas the HHS action plan summarizes the department's work to improve maternal health, The Surgeon General's Call to Action to Improve Maternal Health outlines strategies and the critical roles everyone—from families to States, Tribes, and local communities to health care providers to health systems to researchers—can play in improving maternal health. Like the HHS action plan, the Surgeon General's call to action takes a life-course approach to improving maternal health by promoting mental and physical health in girls and women before and throughout their reproductive years.

The Surgeon General's practical suggestions for families include encouraging healthy behaviors, such as exercise, smoking cessation, regular health care appointments, and breastfeeding; promoting the positive involvement of men as fathers and partners during pregnancy and childbirth and after delivery; and learning the warning signs of potential maternal health issues. Local-level recommendations include adopting policies to support breastfeeding in the community and workplace as well as an evidence-based classification system for maternal care to ensure that women and infants receive risk-appropriate care and a wide range of quality health care options. Providers and health systems can ensure quality preventive care; address racial, socioeconomic, geographical, and age-related disparities; provide culturally appropriate clinical care; help manage chronic conditions; participate in quality improvement and safety initiatives; and encourage trained obstetric care providers to work in underserved areas. Investigators can advance a research agenda that includes developing and testing clinical interventions to address risk factors and identifying inequities within health systems, processes, and clinical practices to reduce disparities. For a complete list of the Surgeon General's recommendations, read the full report.

The Future of U.S. Maternal Health

The HHS plan and Surgeon General's call to action bring renewed attention to the problem of MMM in the United States. In addition, the Biden administration has indicated that future efforts in this area may follow the successful model of the California Maternal Quality Care Collaborative (CMQCC), a public-private partnership for improving maternal health and reducing maternal deaths.[10,11] (See issue 2.1 of *Women's Health in Focus at NIH*, "California Realizes Declining Maternal Mortality," page 5.) These efforts complement NIH's and other initiatives to curb the MMM problem (see *Additional MMM Resources and Initiatives,* page 6) and will address the effects of the COVID-19 pandemic on maternal health (see *COVID-19 and Maternal Health*, page 7). ORWH remains hopeful that collectively, these endeavors will meet the targets of the HHS action plan and "make the United States one of the safest countries in the world for women to give birth."

Thanks to Beda Jean-François, Ph.D., and Gina Roussos, Ph.D., of NIMHD and Pamela Stratton, M.D., of ORWH and the National Institute of Neurological Disorders and Stroke (NINDS) for their help in preparing this article.

Additional MMM Resources…

- The ORWH MMM web portal (www.nih.gov/women/maternalhealth) provides information for women on maternal health, pregnancy-related complications, chronic conditions, pregnancy loss, and other topics; lists relevant publications and ongoing NIH-supported studies on MMM; and links to MMM information from across NIH.
- A special issue of the *Journal of Women's Health*, guest-edited by ORWH Associate Director Samia Noursi, Ph.D., offers multiple scholarly perspectives on MMM.[12] See also "The Intersection of Maternal Morbidity and Mortality and Intimate Partner Violence in the United States," by Dr. Noursi and colleagues.[20]
- The 4th Annual NIH Vivian W. Pinn Symposium, titled "Improving Maternal Health: Behind the Numbers" and held May 15, 2019, featured several scholarly presentations and panels on MMM. A videocast of the symposium is available.
- The HHS Maternal Health webpage collects resources, news items, and other materials for the biomedical research community and the public.
- ORWH Director Janine A. Clayton, M.D., FARVO, has written several "Director's Messages" on topics related to MMM, including "Toward an Improved Vision for Maternal Health and Pregnancy Outcomes," "ORWH Contributes $1 Million to NIH HEAL Initiative to Evaluate Impact of Opioids on Human Development," and "Black Maternal Health: Amplify the Conversation and Act."
- NICHD and ORWH hosted the "Pregnancy and Maternal Conditions That Increase Risk of Morbidity and Mortality Workshop" on May 19–20, 2020, and videocasts of day 1 and day 2 of the event are available.

…and Initiatives

- The NIH PregSource website invites mothers to share their pregnancy stories through a confidential online platform and aims to improve our understanding of pregnancy by gathering information with free questionnaires.
- The Hear Her campaign supports efforts by the Centers for Disease Control and Prevention (CDC) to prevent pregnancy-related deaths by sharing potentially lifesaving messages about urgent warning signs.
- CDC's Enhancing Reviews and Surveillance to Eliminate Maternal Mortality (ERASE MM) program supports agencies and organizations that coordinate and manage maternal mortality review committees (MMRCs) to identify, review, and characterize maternal deaths and identify prevention opportunities.
- The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), established by the 21st Century Cures Act, advises the Secretary of HHS regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. PRGLAC is currently implementing 15 recommendations made in a 2018 report.
- The Pregnancy for Every Body initiative aims to educate plus-size pregnant women about healthy pregnancy and the importance of working with a health care provider to develop a pregnancy plan.
- The Birth Settings in America study, supported by NICHD through the National Academy of Sciences, describes the impact of different birth settings and other social factors on MMM.
- The March of Dimes has partnered with HHS to address MMM disparities and negative maternal outcomes for Black women through the implementation of evidence-based best practices to improve health care quality in hospital settings.
- The Maternal and Infant Health Initiative of the Centers for Medicare and Medicaid Services supports State Medicaid and Children's Health Insurance Program (CHIP) agencies to improve maternal and infant health outcomes.
- The Maternal Morbidity and Mortality Data and Analysis Initiative of the HHS Office on Women's Health works to improve maternal health data collection and to create a network of at least 200 hospitals to deploy clinical, evidence-based best practices in maternity care.

COVID-19 and Maternal Health

The pandemic has affected virtually all aspects of public health—including maternal health, the health care system, health disparities, and biomedical research. While future and ongoing research will continue to assess the extent of COVID-19 on maternal health, initial findings include the following:

- Pregnant women with COVID-19 are at an increased risk of preterm birth, preeclampsia, blood clots, in-hospital death, and other complications, though the incidence of these complications is low.[13,14,21,22]
- Both pregnant and nonpregnant women have experienced higher levels of mental health problems during the pandemic.[15] Research from Wuhan, China, shows increases in depressive and anxiety symptoms among pregnant women since the beginning of the pandemic.[16,17]
- During the pandemic, the risk of adverse outcomes, such as perinatal depression, has been especially high for pregnant women from underserved populations, who already face access barriers to prenatal, intrapartum, and postnatal care.[18]
- The disproportionate impact of COVID-19 on populations that experience health disparities has brought national attention to the importance of social determinants of health, such as overcrowded communities, limited income, frontline employment, food insecurity, and underlying comorbidities. These challenges have further exacerbated health disparities, including maternal health disparities, and have complicated mitigation and prevention efforts to curb transmission of the virus.[8]
- The pandemic has also restricted access to and use of quality health care, including prenatal, intrapartum, and postnatal care. Increased reliance on telehealth services disadvantages those without an internet connection.[8] Survey research indicates that 41% of approximately 5,000 respondents reported avoiding or delaying medical care because of COVID-19 concerns. Notably, nearly a quarter of Black/African American and Hispanic/Latino respondents reported delaying or avoiding urgent medical care, compared with only 7% of White respondents.[19]

Additional information on COVID-19 and maternal health is located on the ORWH MMM web portal and COVID-19 Treatment Guidelines: Special Considerations in Pregnancy.

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Research Demonstrates Disparities in Maternal Health Outcomes, Suggests Actionable Solutions

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Accurately assessing health differences and health equity requires consideration of policy issues and systemic disadvantages.[1,2] One of the greatest health equity challenges of the past two decades has been maternal morbidity and mortality (MMM). Unlike its peer countries, the United States has seen upward trends in the rate of maternal mortality, including deaths occurring in the "fourth trimester"—the 6 weeks after delivery. Data from the Centers for Disease Control and Prevention (CDC) show that about 700 women experience pregnancy-related death each year. An additional 50,000 have severe maternal morbidity, life-threatening complications sometimes referred to as "near misses."[3-5] Persistent troubling racial and ethnic disparities also exist, with African American/Black, American Indian/Alaska Native women, and mothers in underresourced rural communities experiencing the highest burden of pregnancy-related deaths.

Regardless of education or income, Black women in the United States have a three- to four-fold higher risk of experiencing pregnancy-related death.[6] In New York City, Black women are 12 times more likely to die from a pregnancy-related cause than White women.[7] American Indian/Alaska Native women are two to three times more likely to die from pregnancy-related causes.[8] Most of these deaths—60%, according to CDC data—are preventable.[4]

Certainly, comorbidities such as hypertension, diabetes, and other chronic conditions contribute to MMM, and some racial and ethnic groups experience higher rates of these conditions.[9] However, broader social determinants of health—such as access to quality health care, healthful food, safe drinking water, safe neighborhoods, good schools, and stable employment—affect both vulnerabilities to chronic disease and MMM disparities.[10–12]

Poverty, one social determinant of health, is higher among African American/Black, Hispanic/Latino, and American Indian/Alaska Native populations, and its burden is substantively different for women.[13] The intersections of race, sex, and socioeconomic status influence the health of women prepregnancy, and biases embedded in the medical system affect women's health care throughout pregnancy.[2]

Bias—implicit and explicit—is an often overlooked barrier that decreases the likelihood of healthy pregnancies and positive birth outcomes for women of color. The Listening to Mothers study, a 2018 population-based study of women's maternity care and childbearing experiences, demonstrated the necessity of accounting for institutional bias and discrimination in addressing the maternal health crisis.[14] Participating women of color, non-English speakers, and women with Medicaid or no health insurance coverage reported discrimination and inattention by hospital staff, including dismissal of pain complaints and other concerns.[14] African American/Black women had more cesarean deliveries than White women (40% versus 29%) and reported lower levels of practical and emotional support, both of which are linked to higher incidence of MMM. Listening to Mothers researchers and other expert commentators have suggested an association between substandard care practices, negative birth experiences, and MMM.[14,15]

To stem the crisis and advance maternal health equity, researchers, clinicians, policymakers, and advocacy groups have identified possible intervention points—all multisectoral and equity-oriented policy, program, and practice initiatives that could be rapidly accelerated from research to practice.[11,12,16] For the current and next generation of providers, interventions should include skilled instruction on provider-patient power dynamics in the health professions, structural racism and its health outcomes, and cultural safety in cross-cultural situations.[5,6,15,17] At the health-system level, experts recommend staff trainings on anti-racism and health equity, structured strategies to increase access to care for all reproductive-aged women, adoption of health equity and care quality surveillance, and multisector community-engaged outreach to affirm cultural differences and minimize community-level negative cultural representations of non-White groups.[2,14,15]

Six in 10 maternal deaths are preventable.[18] Every actionable strategy to prevent poor maternal outcomes must be implemented. We cannot afford to wait any longer.

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Journal of Women's Health Special Issue Discusses Maternal Morbidity and Mortality

(Various Authors. 2021. J. Womens Health (Larchmt.). *Special Issue.)*

A special issue of the *Journal of Women's Health* (*JWH*) characterizes the increasing problem of maternal morbidity and mortality (MMM) in the United States. Articles in the issue suggest solutions and propose a research agenda for understanding, treating, and preventing maternal health complications.

ORWH Associate Director for Science Planning, Policy, and Analysis Samia Noursi, Ph.D., proposed and served as the guest editor for the *JWH* special issue. Dr. Noursi wrote the introduction to the special issue with colleagues Janine Austin Clayton, M.D., FARVO, Associate Director for Research on Women's Health at NIH and Director of ORWH; Diana W. Bianchi, M.D., Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD); and Dorothy Fink, M.D., former Deputy Assistant Secretary for Women's Health at HHS and Director of the HHS Office on Women's Health. The authors state that the articles describe "epidemiological patterns and trends, biological and physiological risk factors, external risk factors, social determinants of health, and proven and potential interventions that are poised to be delivered to a broader audience."

Maternal Health Disparities in U.S. Subpopulations. Several *JWH* articles discuss how many U.S. subpopulations—including racial and ethnic minorities, transgender individuals, and women of advanced maternal age—have higher rates of MMM as a result of socioeconomic disadvantages, comorbidities, implicit bias, and other factors. Joia Crear-Perry, M.D., and colleagues discuss how influences on the health care system—including individual, clinical, behavioral, social, historical, systemic, structural, and political determinants—and their intersection with race, class, and gender contribute to the problem of MMM. An article by Jennifer L. Heck, Ph.D., and colleagues reviews the available literature on MMM in American Indian and Alaska Native women; identifies hemorrhage, cardiomyopathies, and hypertensive disorders of pregnancy as leading causes of maternal mortality in this population; and points to the numerous knowledge gaps on MMM in this group. Juanita J. Chinn, Ph.D., of NICHD and colleagues describe persistent MMM health disparities among Black women relative to other U.S. women and discuss associated comorbidities and relevant structural inequities within and outside of the health care system. Finally, former ORWH graduate intern Bani Saluja, M.P.H., and former ORWH research scientist Zenobia Bryant, Ph.D., discuss implicit bias and its contribution to racial disparities in MMM in the United States.

Comorbidities and MMM. Women with medical conditions predating conception or conditions that emerge during pregnancy experience higher rates of MMM than women with no comorbidities. Several articles in the special issue of *JWH* discuss how the risk of MMM increases as the result of co-occurring conditions such as dysglycemia, physical and cognitive disability, cardiovascular disease, perinatal depression, sleep-disordered breathing, and infection. Several articles also discuss evidence-based clinical practices for monitoring and treating such patients before, during, and after pregnancy.

Additional MMM Considerations. The *JWH* articles also explore other factors contributing to and issues associated with MMM, including homicide, suicide, drug overdose, and intimate partner violence; environmental factors; and dietary supplements during pregnancy. ORWH Special Advisor David A. Thomas, Ph.D., and colleagues discuss pain and pain management during pregnancy.

An article by ORWH Senior Program Officer Régine Douthard, M.D., M.P.H., and colleagues considers the problem of MMM in a global context.

Addressing the Problem of MMM. Two articles focus on current and proposed efforts to mitigate the problem of MMM in the United States. Catherine Squire Eppes, M.D., and colleagues describe the implementation of new clinical tools and protocols, or "care bundles," designed to improve obstetric safety. An article by Beda Jean-François, Ph.D., and colleagues discusses how existing health information technologies could be leveraged to address health disparities in MMM stemming from racial, ethnic, socioeconomic, and geographical factors.

A New Research Agenda. Michael Lu, M.D., and Dr. Noursi discuss all articles and conclude the *JWH* special issue by proposing a new MMM research agenda for the biomedical community. Synthesizing the contents of the *JWH* articles, Drs. Lu and Noursi identify four key questions indicating where scientific knowledge is lacking: (1) Why are some populations at higher risk for MMM? (2) How can we prevent pregnancy complications and their long-term effects? (3) How can we improve the safety and quality of maternity care? (4) What are the social, structural, and environmental determinants of maternal health? These questions suggest an agenda for the next stages of research and provide a guide to biomedical investigators, policymakers, and funding organizations addressing MMM.

Precision Medicine Should Incorporate Sex- and Gender-Based Clinical Decision-Making

(Review article by Bartz et al. 2020. JAMA Intern. Med. *PMID: 32040165.)*

Deborah Bartz, M.D., M.P.H., and colleagues from Brigham and Women's Hospital and Harvard Medical School recently published a review of scientific

literature supporting the benefits of clinical practices informed by considerations of individual patients' gender identity and sex. Research efforts have identified numerous ways in which biological, social, and environmental factors related to gender and sex affect human health and disease. However, these findings have yet to inform clinical decision-making in a systematic way.

The authors describe eight medical domains in which sex and gender could inform the treatment of individual patients: genetics, epigenetics, hormones, immune function, aging and neurocognitive decline, vascular health, response to therapeutics, and gender and its intersection with the health care system. Acknowledging that this list is not exhaustive, the authors provide a wide set of examples of how sex and gender play roles in these domains and could inform precision medicine. For instance, both sex and gender influence bone health. Men and women have different rates of osteoporosis and associated fractures. Risk factors are related to bone size, muscle mass, estrogen levels, and estrogen and testosterone replacement therapy. Interestingly, transgender women have lower bone density than cisgender men, and transgender men have higher bone mass than cisgender women—evidence of an interaction between sex hormones and gender.

Throughout the article, numerous examples of this type indicate how sex and gender influence health both independently and together in complex interactions. The authors conclude by calling for greater consideration of sex and gender by health care providers, researchers, and medical educators but acknowledge the challenge of doing so, given historical medical practices; the recency of the literature reviewed; the difficulty of studying gender, particularly nonbinary gender identities; and many knowledge gaps.

Sex Affects Gene Expression in Human Tissue

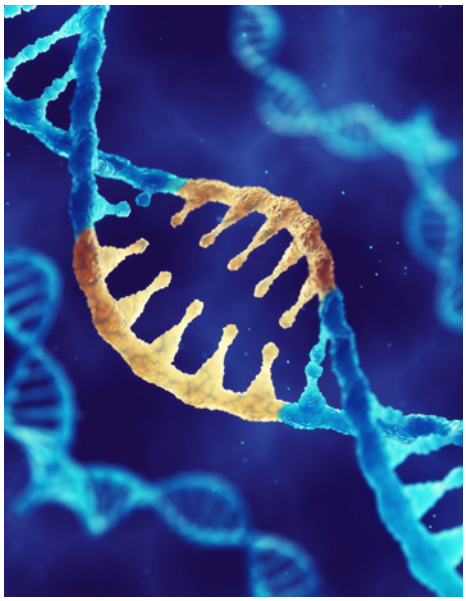
(Original articles by Lopes-Ramos et al. 2020. Cell Reports PMID: 32579922, Oliva et al. 2020. Science PMID: 32913072, and Wilson. 2020. Science PMID: 32913086.)

Findings from two recent studies of genes and human tissues demonstrate that sex exerts a broad influence on gene expression, the process by which genes direct the synthesis of proteins and other products. Both studies involved the analysis of genetic information contained in samples from the Genotype-Tissue Expression (GTEx) Program, an extensive project investigating how DNA variation influences gene expression in human tissues.

In their analysis of GTEx samples, Meritxell Oliva, Ph.D., Barbara E. Stranger, Ph.D., and colleagues detected sex differences in the expression of 37% of genes in at least one of the 44 human tissue types studied. These sex-specific effects in gene expression, though small, were genome-wide. Moreover, the investigators identified over 13,000 sex-biased genes involved in many biological functions. The study also identified cell type–specific sex differences in tissue composition as well as complex interindividual variation in gene expression between the sexes.

A commentary by Melissa A. Wilson, M.D., Ph.D., on this study emphasizes the importance of the investigators' findings. The work of Dr. Oliva and colleagues advances the understanding of how sex and genetics interact to affect human traits, disease, and health. Dr. Wilson also posits that the findings from Dr. Oliva and colleagues may inform the development of new disease therapies and help to explain the sex-specific prevalence of autoimmune disorders, some cancers, and other diseases.

A related study by Camila M. Lopes-Ramos, Ph.D.; John Quackenbush, Ph.D.; Dawn L. DeMeo, M.D., M.P.H.; and



colleagues may also help to elucidate sex differences in many diseases and therapeutic responses. Similar to the study by Dr. Oliva and colleagues, the research by Dr. Lopes-Ramos and colleagues examined how transcription factors—protein molecules that regulate genes by turning them on and off—target specific genes in a sex-biased manner and analyzed over 8,000 GTEx samples from 29 types of healthy tissue provided by 548 individuals. In addition, these researchers built gene regulatory networks that incorporated transcription factors, target genes, and protein-protein interactions for each tissue to compare male and female differences. This systems-based approach synthesizes multi-omics data to gain an integrated insight into the molecular basis of sex differences. Using this model, the investigators determined that 70% of the differentially *regulated* genes examined were not differentially *expressed*. This finding could have been overlooked had the study considered only differentially expressed transcripts. These results deepen the understanding of sex biases in many types of disease and responses to medical treatment and emphasize the need to improve on analytical methods to increase our understanding.

Thanks to Marquitta White, Ph.D., of the National Heart, Lung, and Blood Institute (NHLBI) for help in preparing this article.

FEATURED RESEARCH AND PERSPECTIVES

Survey Research Links Surgeons' Career Satisfaction with Personal Life Factors

(Original article by Johnson et al. 2020. JAMA Surg. PMID: 32579211.)

In response to the high incidence of physician burnout, Michelle R. Brownstein, M.D., and colleagues surveyed 3,807 U.S. surgeons about their career satisfaction, personal lives, medical training, professional choices, and other topics. Data showed that among surgeons, women had lower levels of career satisfaction than men, with 77% of women and 82% of men reporting career satisfaction. Workplace support of work-life integration was the primary factor associated with job satisfaction, particularly among women. Half of women and 45% of men reported having work-related interruptions to their personal lives. Insufficient time for family was associated with lower career satisfaction, but increasing age was associated with higher satisfaction.

Based on these findings, the researchers conclude that optimizing work-life integration might decrease instances of physician burnout, improve the quality of health care, increase productivity, improve the well-being of the surgical workforce, and foster gender equity among surgeons.

Scientists Call for Greater Racial Diversity in Cancer Research

(Commentary by Brady and Weeraratna. 2020. Cancer Discov. PMID: 32816861.)

In a recent issue of *Cancer Discovery*, Donita C. Brady, Ph.D., and Ashani T. Weeraratna, Ph.D., outline many of the barriers facing individuals from underrepresented racial and ethnic groups, particularly Black individuals, in biomedical research. These obstacles impede the professional development of scientific investigators and prevent underrepresented people from participating in clinical studies, particularly those with the potential to improve our understanding of health conditions disproportionately affecting people of color, such as breast, lung, and prostate cancers. As they describe these challenges, Drs. Brady and Weeraratna propose several solutions.

To date, programs designed to address the underrepresentation of some demographic groups in biomedical research have focused on the professional pipeline and on recruiting secondary students and undergraduates into scientific degree programs. However, over recent decades, the number of individuals from underrepresented racial and ethnic groups earning Ph.D.s has increased by a factor of 9.3 (as opposed to a factor of 2.6 for White individuals) without a corresponding increase in the number of assistant professors. Thus, though maintaining investment in pipeline recruitment has value, programs that facilitate the transition from education to career could have greater impact.

In addition, socioeconomic barriers and historically based mistrust can deter underrepresented groups from participating in biomedical research. The authors posit that community outreach, building trust between underrepresented communities and medical institutions, and increasing the number of physicians from underrepresented groups—particularly in the fields of hematology and oncology—might increase the diversity of study participants. Drs. Brady and Weeraratna conclude by encouraging researchers, educators, and others to address these disparities and by recommending several anti-racist resources, such as websites, movies, television programs, and podcasts.

Investigators Address Professional Recognition of Mid-Career Women Physician-Researchers

(Perspective by Lewiss et al. 2020. J. Womens Health (Larchmt). PMID: 31593525.)

A recent editorial by Resa E. Lewiss, M.D., and colleagues reviews how the culture of the biomedical research community can render mid-career women academic physicians professionally "invisible," prompting many to leave the field. Data show that women make up more than half of the health care workforce but remain underrepresented in leadership positions and on medical journal editorial boards. Women physician-scientists receive fewer research grants from funding institutions, are less likely to be listed as lead authors in scientific publications, and have fewer speaking engagements at medical and research conferences. Further, women receive lower salaries than men in comparable physician-researcher positions.

Dr. Lewiss and colleagues also explore less measurable factors that can hamper women's careers in academic medicine. Repeated small instances of gender bias—unconscious or otherwise—and gender-based microaggressions can function to impede career advancement of women by small degrees. Family commitments can hinder women's careers, as can stigma

associated with using maternity leave and other work-life accommodations. Sexual harassment continues to undermine women physician-scientists' professional attainment and health. Dr. Lewiss and colleagues suggest that the accumulation of these factors by the mid-career stage hampers women's professional recognition and advancement, constituting a form of systemic bias and a lack of meritocracy.

The authors suggest several solutions and note several initiatives that could help to improve women physician-researchers' visibility and success, such as top-down interventions like the Athena Swan Charter, gender bias training, mentorship and sponsorship programs, and leadership training.

SCIENTIST SPOTLIGHT

Namandjé N. Bumpus, Ph.D.

Namandjé N. Bumpus, Ph.D., is the E.K. Marshall and Thomas H. Maren Professor and the Director of the Department of Pharmacology and Molecular Sciences at the Johns Hopkins University (JHU) School of Medicine. She earned a bachelor's degree in biology at Occidental College and then a Ph.D. in pharmacology at the University of Michigan. She completed postdoctoral training at the Scripps Research Institute in La Jolla, CA, and then joined the JHU faculty as an assistant professor. Her research laboratory uses mass spectrometry to understand how drug metabolism influences drug outcomes on a mechanistic level. In May 2020, Dr. Bumpus was promoted to her current position and became the first African American woman to chair a department at the JHU School of Medicine.

What are your goals as the Director of the Department of Pharmacology and Molecular Sciences at JHU?

In addition to partnering with faculty, staff, students, and fellows in our department to strengthen the future of research and education in pharmacology at JHU, my ultimate goal is to create opportunities within science for others. As part of this goal, I aim to raise awareness of the challenges that people from historically marginalized groups face in science. I have a responsibility to lend my voice to create an understanding of where improvements need to be made to make science more inclusive. Also, I want to develop partnerships with other biomedical research institutions to build a collaborative network focused on transitioning fellows from historically marginalized groups to well-resourced faculty positions in basic science.

Why do we need more diversity in science, technology, engineering, mathematics, and medicine (STEMM) leadership?

As the saying goes, "If I can't see it, I can't be it." To develop a personal identity within STEMM, emerging scientists need to be able to see people who look like them working in STEMM careers. Representation builds confidence, and confidence gives self-esteem a place to grow. We need diverse representation at all levels of STEMM, including leadership. To strengthen the future of STEMM, we need leaders from a range of backgrounds to be involved in discussions and decision-making. Without this diversity, we risk making decisions—perhaps unintentionally—that are exclusionary and do not benefit all.

How will your tenure as Director contribute to increasing diversity in medicine and related fields?

I hope that through service as a mentor, leader, advocate, and example, I will encourage others to pursue science and persist in science. I also plan to lead and contribute to initiatives that will lead to hiring of faculty from historically marginalized groups as well as career development opportunities for students and postdoctoral fellows from these backgrounds.

What are the barriers to women in science, particularly women of color?

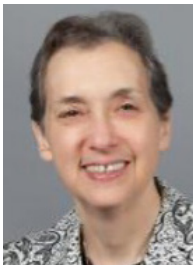
There are many barriers. For instance, societal stereotypes about women, including those specific to women from historically marginalized ethnic groups, extend into STEMM. These stereotypes can result in women being discouraged from pursuing science as students and at the earliest stages of their careers. These biases can also prevent the hiring and promotion of women in science. Those who do persist and establish careers in STEMM have to work in spaces where role models and support systems are scarce. Additionally, sexism and racism influence day-to-day interactions with colleagues and leaders, which can make it difficult to thrive and develop a sense of belonging in science.

Do you have advice for young women scientists?

Don't internalize other people's opinions of what you are (or are not) capable of accomplishing and contributing. At every step of my scientific career, I was told that I would never get to the next step. As an undergrad, I was told I would never make it to grad school. In grad school, I was told I didn't have a future in academia. Once I was a faculty member, I was told I would never earn a leadership role. Tune it all out and stay true to who you are. Focus on the contribution that you want to make to the world. You own your career. No one else does.

IN CASE YOU MISSED IT

NINDS Deputy Director Comments on Her "Rocky Road" as a Woman Scientist



Nina Schor, M.D., Ph.D.

Nina Schor, M.D., Ph.D., Deputy Director of the National Institute of Neurological Disorders and Stroke (NINDS), published a short retrospective of her scientific career to date in *JAMA Neurology*. In it, she describes facing sexism and bias in numerous professional contexts and expresses her hope that future scientists will face a "smoother rocky road" as they pursue careers in STEMM.

Science News Graphically Demonstrates Black Underrepresentation in STEMM

A recent *Science News* article, "These 6 Graphs Show That Black Scientists Are Underrepresented at Every Level," describes the disproportionately low percentages of Black individuals in STEMM fields in higher education and the workplace. A series of simple graphs presents data from the National Science Foundation's National Center for Science and Engineering Statistics (NCSES) and demonstrates that Black students and professionals are underrepresented in most categories associated with STEMM education and employment.

Black Applicants Face Challenges When Interviewed for Medical Positions

In a recent perspective article in *The New England Journal of Medicine*, Josh Ellis, M.D., and colleagues describe the barriers and biases Black applicants face in interviews for medical positions at the student, resident, fellow, and faculty levels. These challenges include microaggressions, stereotypes, tokenism, imposter syndrome, and homophily, which is the sociological tendency for people to connect to those with similar backgrounds and interests, a phenomenon that favors White applicants. The authors suggest several strategies to improve equity throughout the interview process: ensuring that academic leaders acknowledge the problem of bias, training interview personnel to understand the challenges Black applicants face and what to do upon witnessing discrimination, recruiting diverse interviewers, and establishing institutional or national databases for applicants to report racism and bias in interviews.

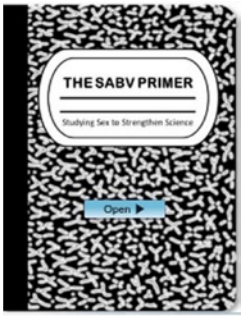
Scientific American Considers the Pandemic's Effects on Academia

"Academia After COVID," a recent article in *Scientific American*, speculates about the long-term effects of the pandemic on academic workplaces, cultures, and classroom models and posits that the pandemic's interruption to university life affords an opportunity for reinvention and improvement. The article considers the benefits and drawbacks of virtual and in-person classes; decreased research productivity, particularly among laboratory scientists; hiring freezes and their effects on early-career scientists; and related topics.

Early-Career Chemists Share the Professional Effects of COVID-19 Lockdowns

A group of junior scientists report on their pandemic-era experiences and insights in a recent issue of the American Chemical Society's publication *ACS Axial*. These early-career researchers describe focusing on family, improving computing skills, researching scientific literature, data analysis, writing papers, organizing online meetings and conferences, and other projects that can be completed at home. The authors also express their hope that news of the pandemic and vaccine development will raise public awareness of the importance of science as well as threats such as future epidemics and climate change.

ORWH Releases E-Learning Courses on Sex and Gender



ORWH recently expanded its e-learning course offerings with "Sex as a Biological Variable: A Primer" and the final two modules of the "Bench to Bedside: Integrating Sex and Gender to Improve Human Health" course. The Sex as a Biological Variable (SABV) primer (also supported by the National Institute of General Medical Sciences [NIGMS] and the NIH Office of the Director [OD]) consists of four independent, interactive modules designed to help the research community—including trainees and researchers at all career stages, NIH grant applicants, and those engaged in peer review—account for and appropriately integrate SABV across all phases of biomedical and biobehavioral research. The "Bench to Bedside" course explores sex- and gender-related differences in key disease areas. The final modules focus on endocrinology and mental health. These and another e-learning course are available, without cost, to all. Visit the ORWH e-learning webpage for more information and to take the courses.

Former ORWH Director Vivian W. Pinn Receives Women in Medicine Legacy Foundation Award

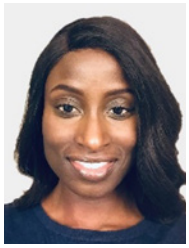
Vivian W. Pinn, M.D.

On November 19, 2020, Vivian W. Pinn, M.D., former Director of ORWH, accepted the Alma Dea Morani, M.D., Renaissance Woman Award, the most prestigious honor bestowed by the Women in Medicine Legacy Foundation (WIMLF), in recognition of her pioneering career in medical science. As the first full-time Director of ORWH, Dr. Pinn spearheaded efforts to include women and minorities in clinical research and to demonstrate the crucial importance of sex differences in biomedical research and health care. Dr. Pinn was also the only woman and only African American to graduate from the 1967 class of the University of Virginia School of Medicine and the first African American woman to chair an academic pathology department in the United States, at the Howard University College of Medicine. You can learn more about the award and its past recipients here.

HHS, NIH, and ORWH Launch New COVID-19 Websites

New websites developed by Federal agencies collect reliable, up-to-date information on COVID-19, issues related to the pandemic, and associated research. The website combatCOVID.hhs.gov, created by the U.S. Department of Health and Human Services (HHS), serves as a central resource for the public and health care providers to find information about different stages of COVID-19 illness, NIH-supported clinical trials to prevent and treat COVID-19, and locations to donate plasma. NIH has launched a website, "NIH COVID-19 Research," that provides the research community and the public with information about research on COVID-19 at NIH and across the NIH-supported research community, including funding opportunities and research news on vaccines, treatments, and testing. ORWH has developed its own COVID-19 webpage, "Women, Science, and the Impact of COVID-19." This webpage discusses sex and gender considerations in COVID-19 research, NIH's support of women in STEMM and biomedical researchers during the pandemic, and the intersections of the *NIH-Wide Strategic Plan for COVID-19 Research* with ORWH mission areas.

ORWH's Nikeya Macioce Makes List of Inspiring Black Scientists



Nikeya Macioce, Ph.D.

ORWH Science Management Analyst Nikeya Macioce, Ph.D., was recently recognized as one of the 1,000 Most Inspiring Black Scientists in America by the Community of Scholars. This list acknowledges the ubiquity and abundance of Black talent in the scientific community, functions to correct the misunderstanding that Black individuals make up a small percentage of outstanding scientists, and provides inspiration to young people excluded because of their ethnicity or race.

Chemist Lectures on Biosensors for Measuring Pain

On January 6, Omowunmi "Wunmi" Sadik, Ph.D., Distinguished Professor and Chair in the Department of Chemistry and Environmental Science at the New Jersey Institute of Technology, gave a lecture, titled "SMART Biosensors: A New Modality to Objectively Quantify Pain," as part of the NIH Director's Wednesday Afternoon Lecture Series (WALS). Nominated for the lecture series by the Women of Color Research Network (WOCRN), Dr. Sadik spoke about her research and development of biosensors and their practical application to help clinicians assess pain objectively. Such tools could complement conventional, more subjective methods of quantifying pain and improve the efficacy and safety of medical pain management. Dr. Sadik's research on biosensors also has applications to environmental, energy, and food safety efforts. A video recording of the lecture is available here.

NOTEWORTHY

Summary Now Available from the NIH Inclusion Across the Lifespan-II Workshop

A summary report from the NIH Inclusion Across the Lifespan-II Workshop: Implementation and Future Directions is now available. This workshop, held virtually on September 2, 2020, brought together pediatric and geriatric experts from a variety of backgrounds in clinical study development and execution. The workshop also considered special populations (e.g., underrepresented racial and ethnic groups, people with disabilities, rural/isolated populations, language-minority individuals, pregnant women, lactating women, people with comorbidities, and sexual and gender minorities) across the life course. This workshop followed up on the first Inclusion Across the Lifespan Workshop, held in June 2017, which focused on barriers to and opportunities for inclusion of children and older adults in clinical studies and informed the development of the NIH Inclusion Across the Lifespan policy, which took effect in January 2019.

NIH Common Fund–Supported Researchers Develop Data Set for Studying DNA Differences

Investigators supported by the NIH Common Fund's Genotype-Tissue Expression (GTEx) program analyzed a large set of human genetic samples and cataloged genetic variants (i.e., differences in the DNA). These genetic variants affect gene expression (i.e., when genes are turned on and off) differently in different tissue cell types throughout the body. A more thorough understanding of these genetic variants could elucidate individual differences in disease risk and in response to drug treatment as well as biological differences between men and women. During the ORWH 30th Anniversary Scientific Symposium, NIH Director Francis S. Collins, M.D., Ph.D., commented on the work of the GTEx researchers. He said, "They found more than 13,000 genes—that's a pretty significant fraction of the total, a little over half—that are expressed differently between the sexes. [...] You simply can't do human research […] without considering sex differences. It's a fundamental part of how biology works." More information on the data set is available here.

UPCOMING EVENTS

53rd Meeting of the Advisory Committee on Research on Women's Health
April 14, 2021
More information is available here.

National Women's Health Week
May 9–15, 2021
More information is available here.

5th Annual NIH Vivian W. Pinn Symposium
May 11–12, 2021
More information is available here.

Intersectionality in COVID-19: Application and Analysis
June 24, 2021 | 1:00 p.m. – 2:00 p.m. (Eastern Time)
More information is available here.

54th Meeting of the Advisory Committee on Research on Women's Health/Consensus Conference Meeting
October 20–21, 2021
More details to come.

Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Annual Meeting
November 1, 2021
More details to come.

For up-to-date information, visit www.nih.gov/women.

FUNDING OPPORTUNITIES

Notice of Intent to Publish a Funding Opportunity Announcement for Advancing Gender Inclusive Excellence (AGIE) Coordinating Center (U54) (NOT-OD-21-051)

Notice of Special Interest: Administrative Supplements and Urgent Competitive Revisions for NIH Grants to Add or Expand Research Focused on Maternal Health, Structural Racism and Discrimination, and COVID-19 (NOT-OD-21-071)

Notice of Special Interest: Small Business Initiatives for Innovative Diagnostic Technology for Improving Outcomes for Maternal Health (NOT-EB-21-001)

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